

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 1 and 69-114 are currently pending in the application, with claim 1 being the independent claim. Claims 63-68 and 115-125 are canceled without prejudice to or disclaimer of the subject matter therein. Claims 2-62 were previously canceled. Claims 1, 76, 91, 96 and 105-107 are amended.

Claim 1 is amended to include the limitations of claims 64-65 and 68, now canceled, and delete reference to phenothiazine-like compounds. Support to the amendment to claim 1 may be found throughout the specification and claims 64-65 and 68 as originally filed.

Claims 76, 91, 96 and 105-107 are amended to delete reference to phenothiazine-like compounds.

These amendments do not introduce any new matter into the application and their entry is respectfully requested.

II. Election/Restrictions

The Office Action, at page 2, demands cancellation of the non-elected claims. Without acquiescing to the propriety of the restriction requirement, the foregoing cancels non-elected claims 63-68 and 115-125.

III. The Rejection Under 35 U.S.C. § 112, Second Paragraph

The Office Action, at page 3, rejects claims 1 and 63-114 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Office alleges that the metes and

bounds of the limitation “phenothiazine-like compounds” are not clear. Applicants respectfully traverse this ground of rejection.

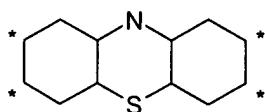
Nevertheless, solely to advance prosecution, and not in acquiescence with the rejection, the foregoing amends the pending claims by deleting reference to phenothiazine-like compounds. Accordingly, the rejection is moot. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

IV. The Rejection Under 35 U.S.C. § 103(a)

The Office Action, at pages 3-5, rejects claims 1 and 63-114 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Nagren *et al.* 1998 *J. Labelled Cpd. Radiopharm.* Vol. XLI, pp. 831-841 (“Nagren”) in view of Link *et al.* 1998 *Eur. J. Nucl. Med* 25(9): 1322-1329 (“Link”). Applicants respectfully traverse this ground of rejection.

A. Summary of the Claimed Invention

The claimed invention is directed to a method of [^{11}C]-radiolabelling a phenothiazine compound having a polycyclic core of the formula:



and a pendant group covalently attached at one of the positions denoted by asterisks (*) in the formula.

B. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

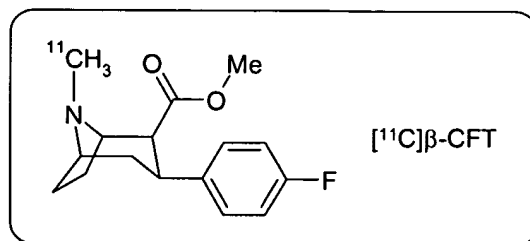
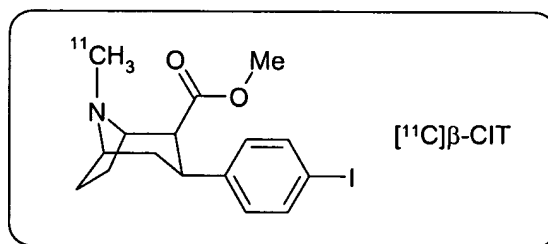
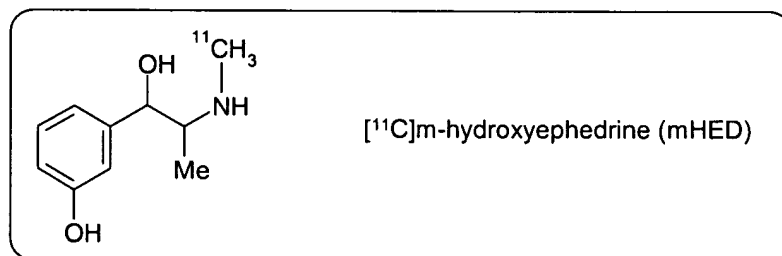
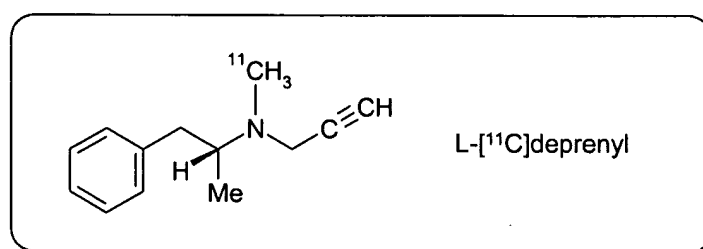
Although Nagren describes [^{11}C]-labelling of certain types of compounds using [^{11}C]methyl iodide (“[^{11}C]MI”) and [^{11}C]methyl triflate (“[^{11}C]MT”), the reference relates to the [^{11}C] radiolabelling of “amides and thiols”, not amines. *See*, for example, the title and “Summary” on page 831; page 832, lines 16 and 18; the examples at page 833, which relate to two compounds which are cyclic amides (NMSP and Flumazenil) and one compound which is a thiol (methionine); and the Conclusion.

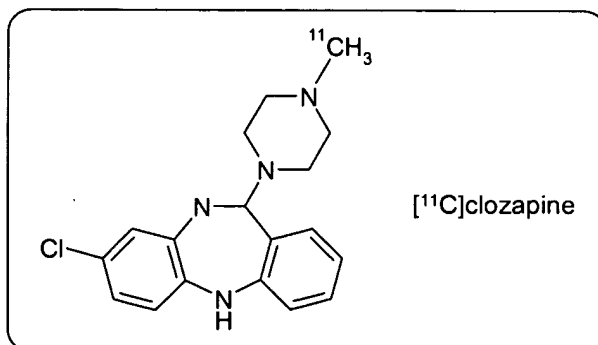
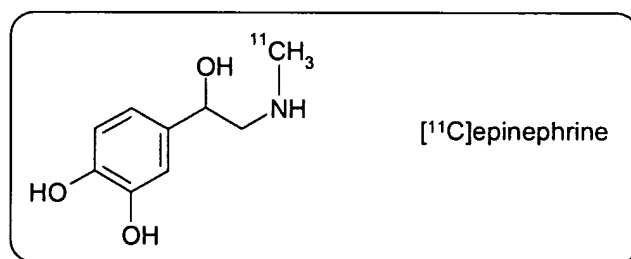
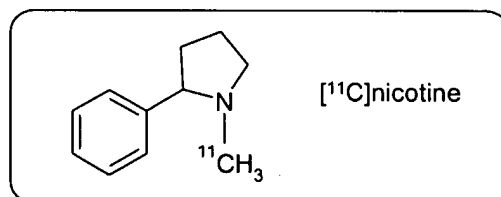
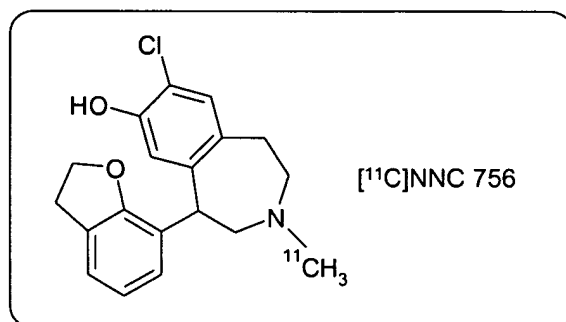
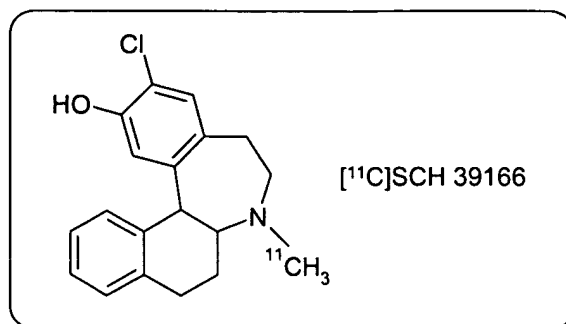
The Office Action, at page 5, alleges that Nagren, at page 837, cites that the preparation of PET radioligands by N-methylation of amines is performed using mild conditions. Applicants wish to point out that, contrary to the Office’s allegation, the work reported in Nagren does not relate to [^{11}C] radiolabelling of amines. In fact, Nagren only discloses the use of [^{11}C]methyl triflate to label the amides NMSP and Flumazenil.

Although Nagren refers to two earlier publications (denoted “4” and “5” therein) which relate to [^{11}C] radiolabelling of amines (*see* lines 2-6 of the first paragraph at page 832), none of the compounds disclosed in the earlier publications has the [^{11}C]radiolabelled amino group attached to an aromatic ring atom, as the compounds in the pending claims. These earlier publications are: (A) Nagren *et al.*, 1995, *Nucl. Med. Biol.*, Vol. 22, No. 2, pp 235-239; and (B) Nagren *et al.*, 1995, *Nucl. Med. Biol.*, Vol. 22, No. 8, pp 965-970.

The (A) document describes the [^{11}C] radiolabelling of the following compounds: deprenyl, m-hydroxyephedrine (MHED), β -CIT, β -CFT, SCH 39166, and α -CIT (the less active anomer of β -CIT). The (B) document describes the [^{11}C] radiolabelling of the following compounds: β -CFT, β -CIT, α -CIT (the less active anomer of β -CIT), SCH 39166, NNC 756, deprenyl, m-hydroxyephedrine (MHED), and nicotine.

Further, Nagren refers to two earlier publications (denoted "6" and "7"), which relate to [^{11}C] radiolabelling of amines (see the second paragraph at page 837). These earlier publications are: (C) Chakraborty *et al.*, 1993, *Nucl. Med. Biol.*, Vol. 20, No. 8, pp. 939-944; and (D) Bender *et al.*, 1994, *Nucl. Med. Biol.*, Vol. 21, No. 7, pp 921-925. Chakraborty describes the [^{11}C] radiolabelling of epinephrine. Bender describes the [^{11}C] radiolabelling of clozapine. The structures of all the compounds disclosed in the earlier publications are provided below:





It is evident that none of the compounds disclosed in Nagren or in the earlier publications cited by Nagren is even similar to a phenothiazine compound as defined in the claims of the present application. As stated above, none of the compounds disclosed in the prior art has the [¹¹C]radiolabelled amino group attached to an aromatic ring atom, as claimed.

Furthermore, as discussed in the description (*see* page 20, lines 12-18), methods known in the art of [¹¹C]radiolabelling Methylene Blue using [¹¹C]methyl iodide failed to produce radiolabelled product (i.e., yields were less than <0.5%), probably because of the necessity to use methyl iodide with a base. It was well known at the time the invention was made that there is a base-catalyzed conversion of Methylene Blue to give Azure B and products of further demethylation. Methylene Blue decomposes slowly in aqueous solutions at pH > 9, and degrades rapidly in 0.01 N NaOH.

None of the compounds exemplified in Nagren and the earlier documents cited in Nagren has an *additional* N-methyl group, as found in Methylene Blue. Accordingly, unlike Methylene Blue, none of the disclosed compounds would be subject to the demethylation side-reaction.

Thus, at least for the reasons stated above, Nagren fails to teach or suggest the claimed invention.

Link does not remedy the deficiencies of Nagren. In fact, Link describes labeling Methylene Blue with the radiolabels [¹²³I] and [¹³¹I] and does not relates to [¹¹C]-labeled Methylene Blue.

Accordingly, the cited prior art fails to disclose each and every element of the claimed invention.

C. There is no Reason to Combine the Elements in the Fashion Claimed

The Office Action, at page 5, maintains that: “*one of ordinary skill would have been motivated at the time the invention was made to develop a method for [¹¹C]-radiolabelling*

methylene blue employing either one of the [^{11}C]-radiolabelling reagents described by Nagren and subsequently use this compound for PET or treating melanoma.” According to the Examiner, allegedly Link provides the motivation for the artisan skilled in the art to [^{11}C]-radiolabel a phenothiazine compound such as Methylene Blue, and Nagren provides the radiolabelling reagent. The Office’s allegation, however, is based on hindsight and is therefore improper.

First, the teachings of Link would not motivate the skilled person to [^{11}C]-radiolabel a phenothiazine compound such as Methylene Blue. In fact, as discussed in the specification (*see* page 2, line 31 to page 3, line 7), Link discloses the use of radio-iodinated Methylene Blue in the detection of melanin in melanoma cells, using gamma camera imaging or positron emission tomography (PET). Link discusses the use of [^{123}I] or [^{131}I], and concludes that the longer-lived isotope, [^{131}I], is preferred because it “further improved the clarity and accuracy of the obtained images”. *See* the paragraph bridging the left and right columns at page 1327. It is noted that [^{123}I] has a half-life ($t_{1/2}$) of 13 hours and that [^{131}I] has a half-life of 8 days. This is notably longer than the half-life of [^{11}C], which is 20.4 minutes.

Accordingly, Link provides a clear teaching away from the use of short-lived isotopes. Nothing in Link would lead the skilled person to consider using much shorter-lived isotopes, such as [^{11}C], which has a half-life that is 38 times shorter than that of [^{123}I] and 565 times shorter than that of [^{131}I]. Quite to the contrary, Link encourages the use of much longer-lived isotopes, such as [^{131}I]. Why would the artisan skilled in the art, despite the clear teaching of Link regarding the use of longer-lived isotopes, be motivated to use a shorter-lived (indeed, 38 times shorter or 565 times shorter) isotope, such as [^{11}C]? Therefore, nothing in Link would motivate the artisan skilled in the art to consider [^{11}C]-radiolabelling a phenothiazine compound such as Methylene Blue.

Second, Nagren and the documents cited therein would not lead the skilled person to expect that a phenothiazine compound such as Methylene Blue could be successfully labeled

using [^{11}C]methyl triflate. Even when, *arguendo*, considering using [^{11}C]methyl triflate, the skilled artisan would expect that the treatment disclosed by Nagren (1.5 aqueous NaOH, heating for 1 minute at 60°C; *see* page 638) or by the earlier documents cited in Nagren would promote demethylation of the product. Accordingly, the artisan skilled in the art, with both the failure of Methylene Blue labeling using [^{11}C]methyl iodide and the base-catalyzed degradation in mind, would **not** be motivated to use [^{11}C] methyl triflate.

Furthermore, because of (1) the teaching away provided by Link with regard to the use of [^{11}C]methyl iodide for Methylene Blue labeling; and (2) the teachings of Nagren with regard to the base-catalyzed degradation, the artisan skilled in the art would **not** expect the successful labeling of Methylene Blue with [^{11}C]methyl triflate.

D. The Present Invention Provides Surprising and Unexpected Results

The present invention surprisingly and unexpectedly provides a method that is fast enough to compensate for the short-life of [^{11}C] and efficient enough to provide sufficient radioactive yield to be useful. The inventors of the present application have shown that, surprisingly and unexpectedly, the use [^{11}C]methyl triflate as a methylating agent greatly increases not only the radioactive yield but also the radiochemical purity of the resulting product. Nothing in the cited documents, whether taken alone or in combination, would have led the skilled person to the claimed invention.

Accordingly, the claimed invention is novel and non-obvious over the cited prior art.

E. The Claimed Invention is not Directed to a Purification Method

The Office Action, at page 5, maintains that: “*The claimed purification methods are routine practices of purification in the field of synthetic chemistry and specific reaction times would fall under routine experimentation and are not considered novel.*” Further, the Office Action, at page 5, asserts that “*Where the general conditions of a claim are disclosed in the*

prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation” (citing In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955)).

In response, it is noted that claim 1 is drawn to “a method of [¹¹C]-radiolabelling a phenothiazine compound”, not a method of purification. In addition, “the general conditions” of the claims are not disclosed in the prior art. Instead, it is only with the benefit of hindsight that the features of the claims can be selected from among the prior art documents and then suitably combined to yield the claimed invention. This does not represent optimization by routine experimentation.

As clearly demonstrated above, the claimed invention is both novel and inventive over the prior art. Accordingly, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

CONCLUSION

All of the stated grounds of rejection have been properly traversed or rendered moot. Thus, the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date

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By

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